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Reference Guide to Mouse Models of Spinal Muscular Atrophy

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Introduction

Spinal Muscular Atrophy (SMA) is an inherited neurodegenerative disease causing progressive loss of motor neurons and is the result of mutation in the *SMN1* gene. SMA is the number one genetic killer of infants and toddlers. Since the mid-1990s researchers in the field of SMA have been developing animal models to aid in the study of the disease. These models are absolutely vital in the process of developing a therapeutic intervention for SMA. At The Jackson Laboratory, our mission is to discover the genetic basis for preventing, treating and curing human disease and we enable research and education for the global biomedical community. The Jackson Laboratory's Rare and Orphan Disease Center distributes the largest collection of SMA related mouse strains. This has been made possible by generous donations from those researchers who engineered the mice and support from the SMA Foundation. By providing a centralized distribution resource for SMA related strains, The Jackson Laboratory facilitates the process of getting the animal models into the hands that need them most: the biomedical research community.

This reference guide is designed to navigate through the history of SMA mouse model development: from the original "work horses" of SMA research developed in the laboratories of Dr. Michael Sendtner at the University of Wurzburg and Dr. Arthur Burghes at Ohio State University to the latest models that allow for the temporal and tissue-specific control of SMN expression as well as new attempts to engineer intermediate models of SMA. It is clear that the evolution of these strains has been achieved by building upon the research discoveries of previous models.

The Jackson Laboratory is home to more than 6,500 strains of JAX® Mice, and our animals are universally recognized as *gold standard* for genetically well-defined laboratory mice. Their stable genotypes and phenotypes are the result of a three component Quality Assurance Program: 1) adherence to the best practices in breeding and colony management, 2) use of molecular testing methods to confirm genetic identity and genotypes, and 3) phenotype monitoring. Why is this important? The results generated in one laboratory should be reproducible in another. The collaborative research environment is by far the most successful—and the tools need to perform consistently across laboratories.

This reference guide will include descriptions of SMA mouse models that have pioneered research in the field along with new models under development; protocols for how to maintain your animals; information on the right animals to choose for your research; and ways you can maintain the genetic and phenotypic integrity of animal models you may develop.

First Generation SMA Mouse Models

Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder characterized by the loss of α motor neurons in the spinal cord and is the leading hereditary cause of infant mortality in humans [1]. Reduced expression of survival motor neuron (SMN) protein is the causative agent in SMA. This reduction in SMN levels is the result of a loss or mutation of *SMN1*. In humans, there is a nearly homologous gene, *SMN2*, differing in only a single nucleotide that has in part some compensatory function. However, a C to T transition in exon 7 of *SMN2* causes an alternative splicing event of this exon and the majority (~90%) of resulting transcript is truncated and non-functional [2]. Because *SMN2* does have the capacity to produce some full length transcript, and thus functional protein, SMA disease severity is dicated by the copy number of *SMN2* [3]. In mice, the genetics are much simpler: there is only one copy of the survival of motor neuron gene: *Smn1*. Loss of this gene in mice leads to embryonic lethality [4]. To model the human condition in mice, one can simply knock out the murine *Smn1* gene, and then genetically add back in varying amounts of human *SMN2* through gene targeting or transgenesis.

The first generation of SMA mouse models, created in the laboratory of Dr. Arthur Burghes, successfully became the pioneers for study of severe Type I, II and III SMA. As depicted in Table 1, "SMA Models-Transgenic Approaches", these three strains (Stock Numbers 005024, 005025 and 005026) collectively became the foundation upon which future models were built.

These three models (005024, 005025 and 005026) illustrate the importance of *SMN2* copy number on survival. As published by Monani et al. in 2000, mice carrying the *Smn1* targeted mutation and a transgene encoding full length human *SMN2*, Tg(SMN2)89Ahmb, are born with normal numbers of motor neurons that become vastly reduced by postnatal day 5 resulting in subsequent death [5]. As evidence supporting the beneficial effect of increasing full length of *SMN2* copy number on survival in the severe model, Dr. Burghes altered this model by incorporating a high copy SMN2 transgene: Tg(SMN2)566, creating Stock Number 008206: FVB.Cg-*Smn1*^{tm1Msd}Tg(SMN2)566Ahmb/J. In this model there are 16 copies of the SMN2 transgene when made homozygous. The extra bolus of SMN2 rescues these animals from overt features of the severe SMA phenotype. However, animals homozygous for the *Smn1* targeted mutation and homozygous for Tg(SMN2)566 transgene do display a shorter and thicker tail [5].

From a model that is very severe to a model that shows no overt phenotype, there are a number of models in between. Stock Number 005025: FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J, or the "delta 7" mouse model, is the workhorse of the research field. The "delta 7" mouse builds on the severe 005024 FVB.Cg-Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J by adding another transgene encoding a human *SMN2* cDNA (SMNdelta7) lacking exon 7 under the control of the human *SMN2* promoter. These animals were originally reported to have a mean survival of 10.2 days with a maximum survival of 16 days [6]. When compared to the survival of the Burghes severe SMA model, Stock Number 005024, it was clear that the addition of the delta 7 transgene had a direct effect on the survival of the animal model increasing lifespan from 5.2 to 13.3 days. This finding was in striking contrast to earlier research claiming that the SMN delta 7 product was pro-apoptotic when produced in the cell and that it had a deleterious effect in SMA[7, 8]. The new data are important because they demonstrate that upregulation of *SMN2* can positively modify the SMA pathology.

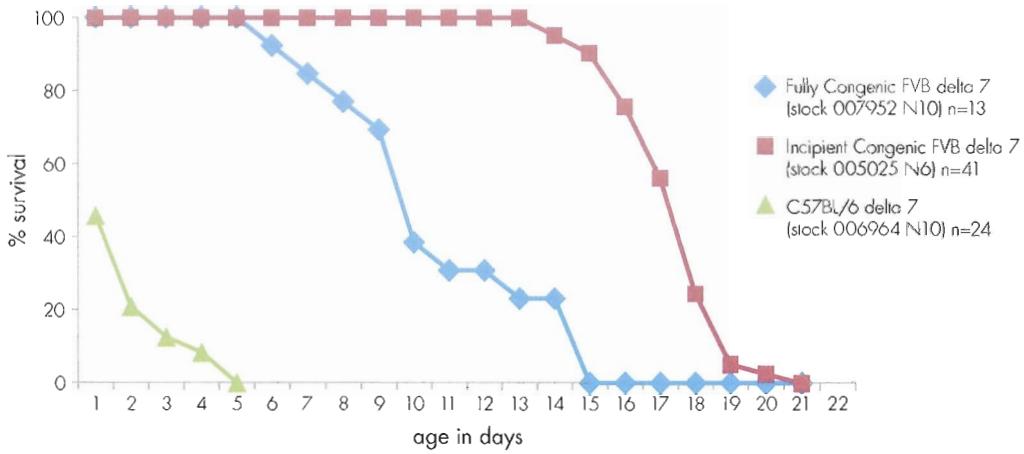
The Importance of Genetic Background

Upon its arrival at The Jackson Laboratory in 2005, the delta 7 mouse was found to be an incipient congenic by high density genome scan, with 15% of the genome typing as non-FVB. After its arrival, this stock was subsequently backcrossed to generate complete congenics on both the FVB/NJ (see Stock Number 007952) and C57BL/6J genetic background (see Stock Number 006964). Phenotypic survival analysis of these crosses demonstrated that genetic background plays a key role in survival of mutant animals. As indicated in the primary publication [9], Dr. Burghes and colleagues had noted that backcrossing with C57BL/6J produced a more severe phenotype. Survival analysis here at The Jackson Laboratory also confirmed these findings. Only 8% of the expected 25% of delta 7 animals generated on a congenic C57BL/6J background survive to birth and as depicted in Figure 1 (labeled as Stock Number 006964) these animals exhibit an extremely early onset of mortality compared to both the FVB incipient congenic (labeled 5025 N6) as well as the FVB fully congenic (labeled as Stock Number 007952 N10).

These findings illustrate the importance of considering genetic background when initiating studies. Generally, alleles of interest (such as spontaneous mutations, targeted mutations, transgenes and congenic regions) are maintained on one to several genetic backgrounds. One background may be more vigorous, better characterized, more amenable to scientific experiments, reproduce better, display a more severe phenotype or have some other advantages over other backgrounds. Inattention to a mutant's genetic background or accidental genetic contamination can seriously confound research results. Each strain has unique background alleles that may interact with and modify the expression of a mutation or transgene directly or indirectly through associated pathways. Even in a well characterized strain, undiscovered modifier

Figure 1

Genetic Background Effects on SMA Phenotype B6 vs FVB: Survival



genes may alter results, sometimes making them hard to explain. Thus as you decide which mouse strain is appropriate for your research, consider its genetic background.

While the delta 7 mouse was being developed, Dr. Burghes and colleagues were also creating mouse models to examine the effects of different variants of SMN on disease pathology. Ideally, tools for SMA research would encompass disease models for all levels of severity. As published, Stock Number 005026 FVB.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb *Smn1*^{tm1Msd}/J animals exhibited a delay in the onset of motor neuron loss, resulting in mice with mild SMA[10]. This animal differs from the delta 7 model in that instead of carrying Tg(SMN2*delta 7)4299Ahmb, it carries a transgene encoding an SMN A2G missense mutation. Interestingly, when the SMN A2G transgene is combined alone with the *Smn1* targeted mutation, it is unable to rescue animals from embryonic lethality. However, when the A2G transgene is coupled with Tg(SMN2)89Ahmb, expressing full length *SMN2*, the animals exhibited a mild Type III phenotype characterized by motor axon degeneration, loss and sprouting; muscle atrophy; and abnormal EMG patterns [10]. In striking contrast to this mild phenotype, it has been the experience at The Jackson Laboratory that the Tg(SMN1*A2G)2023Ahmb transgene is unable to fully rescue the embryonic lethality on the C57BL/6J background (see Stock Number 007222). In addition, the original Stock Number 005026 phenotype appears to be even more mild than previously described, as noted by survival and less discernable muscle weakness. Although it is unclear as to the reason for the drift in phenotype, changes in genetic background are likely to account for the milder phenotype.

Table 1 "SMA Models-Transgenic Approaches" illustrates the many different genetic versions of the original Burghes lines: Stock Numbers 005024, 005025 and 005026. We have indicated where there are known genetic background differences. Other models that were developed in a similar manner to the Burghes lines include Hung Li's mild Type III model: Stock Number 005058 FVB.Cg-*Smn1*^{tm1Hung} Tg(SMN2)2Hung/J. In comparison to the consistent early lethality phenotype in the Burghes severe model, Stock Number 005024, Li's model carrying a transgene encoding a full length SMN2 (Tg(SMN2)2Hung) was reported to have severe, intermediate and mild SMA phenotypes all occuring within the same litter [11]. This phenomenon was clarified in a later publication by DiDonato et al. that reasoned multiple levels of disease severity within a litter was observed in the original Li publication because animals hemizygous for the Tg(SMN2)2Hung transgene and heterozygous for the *Smn1*^{tm1Hung} targeted mutation were intercrossed, creating progeny that was hemizygous, homozygous or wild-type for the transgene. As expected, animals carrying varying copies of the transgene exhibited differing levels of disease severity [12]. The one aspect regarding the Li model that remained unclear was how animals hemizygous for Tg(SMN2)2Hung and homozygous for the *Smn1*^{tm1Hung} targeted mutation exhibited varying levels of phenotypic severity. One hypothesis is that the original animals in the Li publication were not fully backcrossed to FVB/N or that the initial observations resulted from transgenes of various founder lines. As evidenced by the original delta 7 animals, genetic background plays a key role in survival and SMA phenotype severity.

In addition to the original lines made by Dr. Arthur Burghes and Dr. Hung Li, another model of severe SMA was developed by a group led by Dr. Thierry Bordet at TROPHOS. Their line combines two transgenes encoding full length *SMN2* at differing copy numbers along with the *Smn1*^{tm1Msd} to generate mutants that begin to lose weight by postnatal day 7, display progressive muscle weakness and an abnormal gait, and eventually succumb to disease at a mean age of 15 days [13]. This model, Stock Number 008631 B6.Cg-Tg(SMN2)11Tro Tg(SMN2)46Tro *Smn1*^{tm1Msd}/J is generated by crossing Stock Numbers 008629 B6.Cg-Tg(SMN2)11Tro *Smn1*^{tm1Msd}/J, and Stock Number 008630 B6.Cg-Tg(SMN2)46Tro *Smn1*^{tm1Msd}/J, both homozygous for their respective transgenes and heterozygous for the *Smn1*^{tm1Msd} targeted mutation. Resulting progeny that are hemizygous for each transgene and are homozygous for the targeted mutation display the published severe phenotype.

Second Generation SMA Mouse Models: The Allelic Series

While the first generation of animal models of SMA provided (and still provide) excellent research tools for elucidating disease mechanisms and aiding in efforts for therapeutic intervention, it was widely recognized that working with multiple transgenes and targeted mutations all segregating independently was somewhat laborious, particularly when one considers combining these models with other potentially disease-modifying targeted mutations or trangenes. Transgenes that insert randomly into the genome come with a host of caveats—these transgenes can be problematic if the spatial and temporal expression of the transgene does not mirror that gene's endogenous pattern which can influence experimental findings [14]. With these caveats in mind, a second generation of SMA mouse models has been developed by using a recombineering approach to target varying copy numbers of *SMN2* directly into the murine *Smn1* locus [15]. As depicted in Figure 2, this approach engineered a hybrid allele consisting of exons 1-6 and human exons 7 and 8 along with either 1 or 3 copies of full length human *SMN2*. It is important to note that the human derived exons 7 and 8 in the hybrid portion of these constructs are derived from human *SMN2*, thus ~90% of the transcripts from this hybrid allele will lack exon 7. Coupled with a knockout allele, it is theoretically possible to generate mice with a total of 0, 1, 2, 3, 4, 5, 6 or 8 copies of *SMN2* (full-length plus hybrid alleles). Interestingly, survival analysis on mutants generated from the allelic series on a mixed genetic background revealed a sharp delineation between embryonic lethality and long lived animals with no intermediate phenotype observed in the series. (see **Table 2: SMA mouse models engineered by targeting *Smn1* locus**).

Each of these alleles arrived at The Jackson Laboratory on a mixed genetic background. They were subsequently backcrossed to both FVB/NJ and C57BL/6J using a speed congenic approach. Initial characterization (body weight and survival) was performed on cohorts mixed genetic background of the allelic series, followed by characterization of combinations of the allelic series. In contrast to the first generation of mice engineered by the Burghes Lab, this allelic series did not display striking differences in phenotype between FVB/NJ and C57BL/6J genetic backgrounds. General phenotypic observations can be found in Table 2.

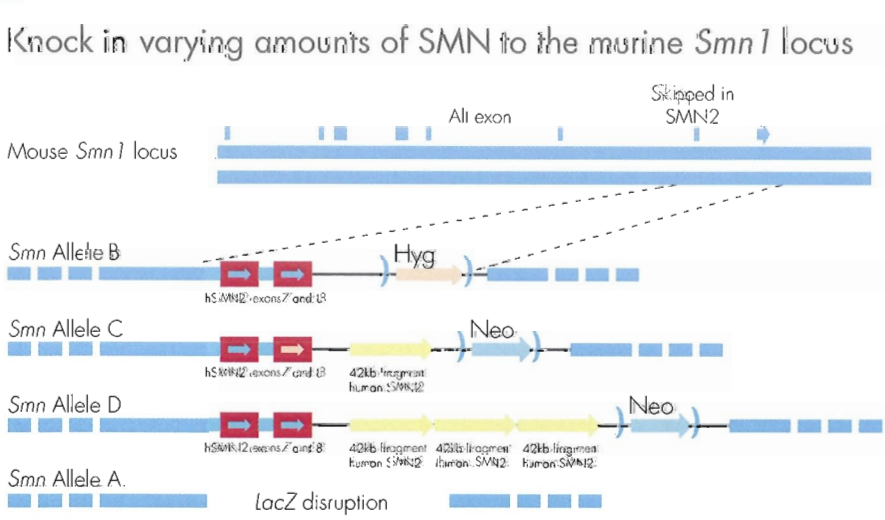


Figure 2 Schematic of Regeneron Allelic Series targeting the murine *Smn1* locus. Red boxes denote human derived genomic segments of the hybrid portion, light blue denotes regions of murine genome.

Conditional Alleles and Site-Specific Expression

Some of the most pressing questions in the SMA research field are: *where* does SMN need to be expressed, *how much* SMN needs to be expressed, and importantly *when* does it need to be expressed to have a beneficial impact on disease pathology. Made by Regeneron, the hybrid rescue allele, *Smn1*$^{tm3(SMN2/Smn1/SMN2)Mrph}$ is engineered to revert to a fully functional *Smn1* allele upon Cre-mediated recombination. To accomplish this, exons 7 and 8 of the mouse *Smn1* (survival motor neuron 1) gene and several hundred base pairs of flanking sequence were replaced with a fragment containing, in order: 1) an inverted *lox71* site; 2) exon 7 from the human *SMN2* (survival of motor neuron 2, centromeric) gene flanked by several hundred base pairs of intron sequence; 3) an inverted copy of mouse *Smn1* exon 7 flanked by several hundred base pairs of intron sequence; 4) a *lox66* site; 5) an *FRT* site remnant from a deleted selection cassette; and 6) human *SMN2* exon 8 including the 3'UTR and polyA signal with several hundred base pairs of flanking sequence. The engineered allele expresses a hybrid *Smn1* gene containing mouse *Smn1* exons 1 through 6 and human *SMN2* exons 7 and 8. The human *SMN2* exon 7 is skipped in the majority of mRNA derived from the hybrid gene due to a single base pair difference in human *SMN2* exon 7, compared to human *SMN1* exon 7. Following Cre-mediated irreversible inversion of the fragment bordered by the *lox71* and *lox66* sites, the allele is "rescued" into a format that contains mouse *Smn1* exons 1 through 7 and human *SMN2* exon 8. Because the mouse *Smn1* exon 8 is efficiently spliced, the majority of the mRNA from the rescue allele after Cre-mediated inversion contains mouse *Smn1* exon 7. The schematic of this construct is depicted in Figure 3.

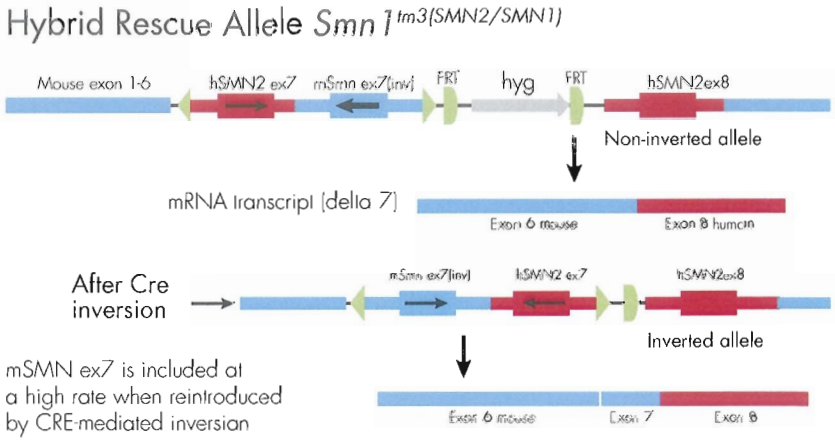


Figure 3. Schematic of the hybrid rescue allele prior to Cre-mediated inversion (upper) and after Cre-mediated inversion. Red denotes regions of human derived genome and light blue denotes regions of murine derived genome. Triangles indicate *lox*^{P} sites.

The utility of the hybrid rescue allele is enhanced by the wide variety of tissue-specific and inducible Cre recombinase alleles available at The Jackson Laboratory. While there are far too many to list here, the complete collection, along with expression data can be found at http://cre.jax.org/index.html. The hybrid rescue allele is available by itself on fully congenic FVB/NJ and C57BL/6J genetic backgrounds (Stock Numbers 007964 and 007966 respectively) as well as in its "rescued" configuration (mediated by EIIa driven Cre recombinase) as Stock Number 008898 (see *Table 3: SMA Strains for testing site-specific SMN expression*).

Because of the vast amount of literature on the delta 7 mouse model, the hybrid rescue allele was transferred to this model by substituting it for *Smn1*^{tm1Msd}. In the non-recombined state this allele is a functional null, and indeed, mortality studies on mutants homozygous for the non-recombined hybrid rescue allele demonstrated a similar survival pattern as the original delta 7 mouse (Figure 4).

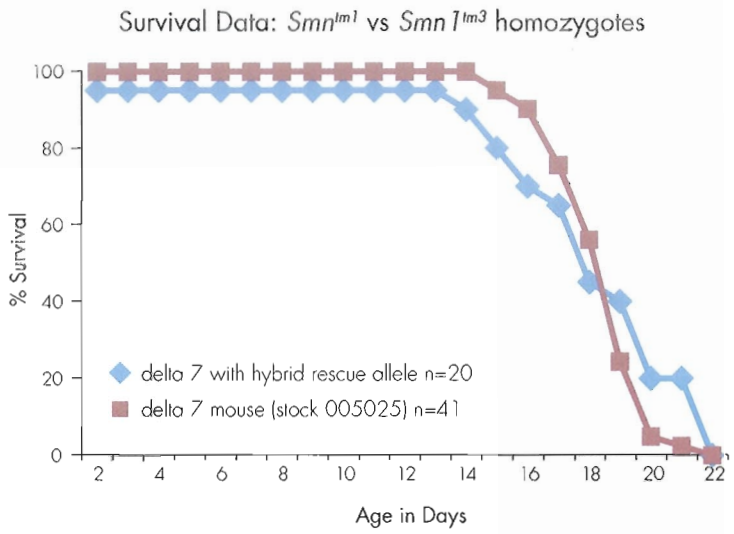


Figure 4. Kaplan Meier survival curve of the delta 7 mouse with the hybrid rescue allele in the non-recombined (functional null) state compared to the original delta 7 mouse.

Whereas the hybrid rescue allele is utilized to discern where SMN needs to be expressed, Dr. Judith Melki's floxed *Smn* allele, also known as *SMN*^{F7}, can be used to test the effects of tissue-specific knock down of SMN expression. Available on a fully congenic FVB/NJ (Stock Number 006138) and C57BL/6J (Stock Number 006146), this allele can be used with a variety of tissue-specific Cre lines to determine the impact of diminishing SMN expression in a site specific manner [16]. If used in conjuction with a temporally controlled (doxycycline inducible or tamoxifen inducible) Cre, one could also examine the effects of knocking down SMN expression at particular developmental timepoints of interest. At The Jackson Laboratory, we have also combined the *SMN*^{F7} allele onto the delta 7 mouse background by substituting this allele for the *Smn1*^{tm1Msd} targeted mutation (see Stock Number 008897).

Listed in **Table 3: SMA Strains for testing site-specific SMN expression** are the various Cre-lox system based research tools exploiting the variety of ways that the hybrid rescue allele can be manipulated to answer many questions pertaining to the location and timing of SMN expression. The Jackson Laboratory has an extensive collection of Cre-expressing lines that can be used in combination with these alleles: http://cre.jax.org/strainlist.html. Accompanying these SMA conditional alleles is also a small collection of strains that utilize tissue-specific promoters to localize SMN expression. All of these strains can be used in conjunction to collectively answer questions regarding where and when SMN needs to be expressed for purposes of therapeutic intervention.

Also of interest to SMA researchers are supportive strains designed to test the effects of modifier genes. For example, Stock Number 006556 harbors a targeted mutation in the *Islet-2* (*Isl2*) gene, whereby Cre-mediated recombination can cause the deletion of Isl-2 expressing cells in tissue-specific manner. Stock Number 007941 combines the delta 7 mouse with a targeted knock-in expressing IGF-1 from the nebulin locus. Studies demonstrated a neuroprotective effect of IGF-1 in animal models of ALS, and this model was developed to observe any similar protective effect in SMA [17].

We have also included Stock Number 006553, the delta 7 "immorto" mouse in this collection of SMA research tools. This animal harbors the Tg(H2-K1-tsA58)6Kio -Immortomouse transgene (from *H-2K*^{b}-tsA58 transgenic founder line 6 (H2ts6)) that allows interferon-inducible expression of a thermolabile large tumor antigen (TAg) (and the small tumor antigen) from the SV40 thermosensitive A58 (tsA58) strain directed to widespread tissues by the interferon-inducible Class I antigen promoter from the mouse *H-2K*^{b} locus. Stock Number 006553 can aid in the development of cell lines for SMA researchers. The complete list of "tool" strains available for SMA research including those to visualize both neurons and SMN localization can be found in **Table 4: SMA Research Tool Strains.**

The Quest For Intermediate SMA Models

Several promising therapeutic strategies for the treatment of SMA are currently being pursued. As these therapies start to move from the research laboratory to the clinic, it becomes imperative to understand how effective these therapies will be after the onset of disease and whether there is a critical window for drug delivery. For many of the therapies in the pipeline, varying degrees of benefit have been demonstrated when treating the severe delta 7 mouse model of SMA at early neonatal time points. However, the rapid kinetics of disease progression in severe mouse models of SMA present several obstacles to preclinical testing of therapeutics. Among these are the narrow window for which intervention has been demonstrated to be successful and the short overall survival time of 17 days. The severe model also does not fully represent the spectrum of disease observed in the patient population, thus lack of efficacy of a potential therapeutic in the severe mouse model of SMA may not necessarily preclude its benefit in a milder form of disease. While most agree that a milder/more intermediate mouse model would be beneficial, generating such a mouse model has proven difficult. Nonetheless, as summarized in Figure 5, the current collection of SMA mouse models has paved the way for several promising therapeutics to enter the clinical development pipeline.

Looking back across multiple efforts by various laboratories to generate SMA mouse models, one can easily notice a pattern with respect to

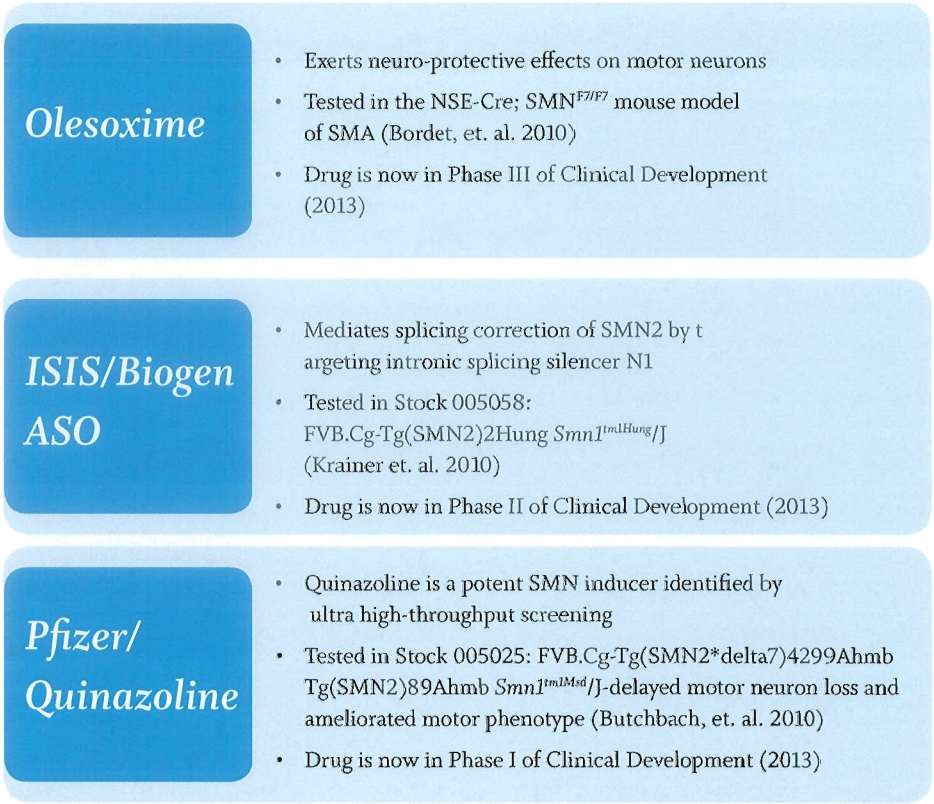


Figure 5: Three drugs that have entered the clinical development phase of FDA approval. Each of these therapeutics have been developed and tested in different types of mouse models of SMA and have different modes of action.

viable phenotypes and SMN levels. The models generated by genetic disruption of the murine *Smn1* locus coupled with transgenic addition of human SMN2 generally fell into three classes: those that died just after birth [5, 13], those that died just at or prior to wean [6], and then to the extreme: mice that lived a normal lifespan with very mild neuromuscular pathology [10, 18, 13]. Thus, there exists a delicate balance in SMN levels that can lead to early lethality or longevity in a mammalian system. A number of labs are currently working to engineer intermediate SMA mouse models. At The Jackson Laboratory, we have combined a number of previously described alleles to develop the Burgheron Model (See Stock 014561 in Table 1). The Burgheron model possesses many similar characteristics of previously described SMA models: an intermediate lifespan, and notable deficits at the neuromuscular junction. Another intermediate model, known as the SMNRT (or "read through" line) was recently published by the Lorson laboratory [19]. Genetically, this model is similar to the delta 7 model; however, the SMN delta 7 transgene has been altered to encode a slightly more functional protein. Importantly, there is not a full phenotypic correction, which allows for the examination of a broad range of therapeutics, including SMN2-dependent and SMN-independent pathways.

In addition to the challenges in titrating SMN levels in mice, there are a number of co-morbidity phenotypes that are found in SMA mice but are not observed in patients. For example, many of the mild models develop abnormalities in the vasculature system that lead to necrosis of the tails, ear pinnae and feet. The necrosis makes it difficult to assess strength in traditional behavioral assays such as rotarod and open field. While the necrosis can be troublesome in this regard, it can serve as a surrogate marker for SMN levels. The amount of tail necrosis inversely correlates with SMN protein levels, so therapies that increase SMN levels can be assessed simply by monitoring the tail length of the treated mice. Other phenotypes noted in mice, including delta 7, include cardiac hypertrophy [20, 21] and other phenomena such as bladder blockage. This evidence suggests that the mice, unlike human patients, have abnormalities that significantly affect the enteric nervous system, which ultimately may be the primary source of death in these mice. Thus, while survival may be a convenient measurement of drug efficacy, it may not be as clinically relevant as, for example, an assessment of the motor unit itself.

Both of these mouse models express slightly more SMN than the delta 7 model, yet their phenotypes range from no mortality, necrosis and mild cardiac and NMJ deficits (Stock 008714 pictured on left) to necrosis accompanied by increased mortality and more profound neuromuscular junction defects (Stock 014561 pictured on right)

Summary

This resource manual summarizes The Jackson Laboratory's extensive resources for SMA research. Its purpose is to guide you through your selection of the best model for your studies. For accurate interpretation of results, it is essential to understand the differences that exist in the spectrum of disease as it is modeled by a mouse — not only on a phenotypic level but on the molecular defect level as well, and recognize that not all phenotypes displayed by mouse models may be relevant in the clinic. Nonetheless, mouse models have proven essential in both basic research and preclinical discovery for bringing promising therapeutics to the clinic for SMA patients.

Support from the SMA Foundation allows us to be able to collect, curate, and genetically standardize these models for the scientific community.

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Table 1: SMA Mouse Models: Transgenic Approaches (★ Indicates top 5 most frequently used of this strain group)

Stock #	Strain Name	Common Name	Mortality (**unpublished)	General Phenotype	Mutant Genotype*	SMA Type
005025 ★	FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J	"Delta 7" mouse incipient congenic	Mean Survival of 17.7 days	By day 5, signs of muscle weakness are apparent and become progressively more pronounced over the following week as the mice display an abnormal gait, shakiness in the hind limbs and a tendency to fall over. Mean survival is approximately 13 days. Immunocytochemical analysis indicates that dystrophin expression is normal, however fibers isolated from the gastrocnemius muscle of a 14 day old triple mutant clearly show evidence of atrophy.	HOM-HOM-HOM	Intermediate
006964	B6.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/UmonJ	"Delta 7" mouse-B6 background	Embryonic-PND5**	"Delta 7" mouse on a C57BL/6J background, much earlier mortality than on FVB/N background; only 8% of the expected 25% mutant animals are noted at birth.	HOM-HOM-HOM	Severe
007952	FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J	"Delta 7" mouse FVB/NJ fully congenic	Mean Survival of 11 days	Fully congenic version of the "Delta 7" mouse on an FVB background, earlier mortality than on the incipient FVB/N background but not as severe as the C57BL/6 background	HOM-HOM-HOM	Intermediate
008206	FVB.Cg-*Smn1*^{tm1Msd} Tg(SMN2)566Ahmb/J	SMN2 high copy line 566	None	High copy of the SMN2 transgene rescues mutants from all overt features of severe SMA, however animals do have a shorter, thicker tail.	HOM-HOM	N/A
009134 ★	FVB.Cg-*Smn1*^{tm1Msd} Tg(SMN2)89Ahmb Tg(SMN2*A111G)591Ahmb/J	SMN2A111G founder 591-spinal cord and weak expression in forebrain and liver	> 1 year	Rescued from all overt features of SMA when homozygous for both transgenes and targeted mutation. Animals homozygous for only the Tg(SMN2*A111G)591 and the *Smn1* targeted mutation are not viable.	HOM-HOM-HOM	N/A
008782	FVB.Cg-*Smn1*^{tm1Msd} Tg(SMN2)89Ahmb Tg(SMN2*A111G)588Ahmb/J	SMN2A111G founder 588-brain, spinal cord and liver expression	> 1 year	Rescued from all overt features of SMA when homozygous for both transgenes and targeted mutation. Animals homozygous for only the Tg(SMN2*A111G)588 and the *Smn1* targeted mutation are not viable.	HOM-HOM-HOM	N/A
005024 ★	FVB.Cg-Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J	Burghes' Severe Model incipient congenic	Stillborn or 4-6 days	Low birth weight, decreased suckling and movement, labored breathing, tremoring limbs.	HOM-HOM	Severe
006773	B6.Cg-Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J	Burghes' Severe Model on C57BL/6J background	Embryonic lethal**	More severe than the original Burghes line; mice are not born.	HOM-HOM	Severe
007949	FVB.Cg-Tg(SMN2)89Ahmb *Smn1*^{tm1Msd}/J	Burghes' Severe Model FVB/NJ congenic	TBD**	Fully congenic version of Stock 005024.	HOM-HOM	Severe
014561	FVB.Cg-Tg(SMN2)89Ahmb *Smn1*^{tm1Msd} *Smn1*$^{tm3(Smn1/SMN2)Mrph}$/J	"Burgheron" Mouse	Peripheral necrosis, cardiac hypertrophy, NMJ maturational delay, electrophysiological defects, shortened lifespan	These animals harbor one copy of the Tg(SMN2)89 and are a compound heterozygote at the *Smn1* locus for the "C" Allele (see Stock 008604), and the null allele (see Stock 006214). These animals have an intermediate level of SMN expression that falls between that of homozygous C allele mutant and Delta 7 mutant mice.	HEMI-CMPD HET	Mild

014559	B6.Cg-Tg(SMN2)89Ahmb *Smn1*^{tm1Msd} *Smn1*$^{tm5(Smn1/SMN2)Mrph}$/J	"Burgheron" Mouse-C57BL/6J genetic background	Characterization underway	These animals harbor one copy of the Tg(SMN2)89 and are a compound heterozygote at the *Smn1* locus for the "C" Allele (see Stock 008714), and the null allele (see Stock 010921). These animals have an intermediate level of SMN expression that falls between that of homozygous C allele mutant and Delta 7 mutant mice.	HEMI-CMPD HET	Mild
005058 ★	FVB.Cg-*Smn1*^{tm1Hung} Tg(SMN2)2Hung *Smn1*^{tm1Hung}/J	SMA-like mice line 2	None	Mice exhibit a molecular and progressive neurodegenerative phenotype similar to Type III SMA.	HOM-HOM	Mild
008629	B6.Cg-Tg(SMN2)11Tro *Smn1*^{tm1Msd}/J	Trophos Lethal Model	Hours-7 days after birth	Mice that die at or shortly after birth are slightly smaller than normal littermates. Mice that survive for several days are indistinguishable from normal littermates in the first 48 hours, after which they exhibit diminished weight gain. Mice hemizygous for the transgene and homozygous for the targeted mutation display an embryonic lethal phenotype.	HOM-HOM	Severe
008630	B6.Cg-Tg(SMN2)46Tro *Smn1*^{tm1Msd}/J	Trophos Rescued Model	None reported	Mice that are homozygous for both the *Smn1*^{tm1Msd} targeted mutation and the SMN2, survival of motor neuron 2, centromeric, human, transgene (founder line 46) are viable, fertile and do not display a SMA-like phenotype. Necrotic lesions are observed on the tail, ears and teeth.	HOM-HOM	N/A
008631	B6.Cg-Tg(SMN2)11Tro Tg(SMN2)46Tro *Smn1*^{tm1Msd}/J	Trophos Severe Model	Mean survival of 15 days	Mice that are homozygous for the *Smn1*^{tm1Msd} allele and hemizygous for the two transgenes, Tg(SMN2)11Tro and Tg(SMN2)46Tro, exhibit symptoms and neuropathology similar to patients afflicted with severe proximal SMA. Triple mutants are indistinguishable from normal littermates in the first 4 days, after which they exhibit diminished weight gain. By 7 days of age, signs of muscle weakness are apparent and become progressively more pronounced over the following week as the mice display an abnormal gait. Mean survival is approximately 15 days although a few animals (<3%) can survive longer.	HEMI-HEMI-HOM	Intermediate
005026 ★	FVB.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb *Smn1*^{tm1Msd}/J	"A2G" mouse, Burghes' Type III Model incipient congenic	Shortened lifespan < 1 year	Published as smaller body weight, diminished activity, muscle weakness, angulated atrophic muscle fibers, reduced number of motor neurons. The Jackson Laboratory notes a milder phenotype than the original publication.	HOM-HEMI-HOM	Mild
007968	FVB.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb *Smn1*^{tm1Msd}/J	"A2G" mouse, Burghes' Type III Model FVB congenic	> 1 year**	Fully congenic version of Stock 005026; characterization underway.	HOM-HOM-HOM	Mild
007222	B6.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb *Smn1*^{tm1Msd}/J	"A2G" mouse, Burghes Type III Model-B6 background	Embryonic-PND21**	Animals homozygous for Tg(SMN2)89, hemizygous for Tg(SMN1*A2G)2023 and homozygous for *Smn1*^{tm1Msd} are born at lower than expected Mendelian ratios with only 6 mice out of 470 animals born. The 1% of animals that survived died by P21.	HOM-HOM/ HEMI-HOM	Severe

* For strains with more than one allele, the genotype designation follows the order of the allele in the strain nomenclature.

Table 2: SMA Mouse Models: Engineered by Targeting *Smn1* Locus (★ Indicates top 5 most frequently used of this strain group)

Stock #	Strain Name	Common Name	Mortality (**unpublished)	General Phenotype	Mutant Genotype*	SMA Type
008604 ★	FVB.129(B6)-*Smn1*$^{tm5(Smn1/SMN2)Mrph}$/J	Regeneron C allele fully congenic FVB/N genetic background	Viable no mortality	This mutant mouse carries the *Smn* allele C, which contains two tandem *Smn1/SMN2* genes. The first is a hybrid gene in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn1* gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene. The second is a full 42 kb copy of the human *SMN2* gene. Homozygous animals exhibit tail necrosis, lower body weight, diminished grip strength, and lower bone mineral content and density with age.	HOM	Mild
008714 ★	B6.129-*Smn1*$^{tm5(Smn1/SMN2)Mrph}$/J	Regeneron C allele C57BL/6J congenic genetic background	Viable no mortality	This mutant mouse carries the *Smn* allele C, which contains two tandem *Smn1/SMN2* genes. The first is a hybrid gene in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn1* gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene. The second is a full 42 kb copy of the human *SMN2* gene. Homozygous animals exhibit tail necrosis, lower body weight, diminished grip strength, and lower bone mineral content and density with age.	HOM	Mild
006214 ★	FVB.Cg-*Smn1*^{tm1Msd}/J	*Smn1* targeted mutation	Embryonic lethal	This targeted mutant allele was created in the laboratory of Dr. Michael Sendtner at the University of Wurzburg, Germany. Exon 2 of the endogenous mouse *Smn* gene was disrupted by employing a targeting vector encoding a neomycin cassette and a *lacZ* gene fused to the first 40 nucleotides of the disrupted exon to permit expression of the *lacZ* gene in tissues where SMN is normally expressed.	HOM	Severe
009378 ★	B6.129-*Smn1*$^{tm6(SMN2)Mrph}$/J	Regeneron D allele, congenic C57BL/6J genetic background	Viable no mortality	*Smn* allele D contains four tandem *SMN* genes. The first is a hybrid gene in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn* gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene. The next three are identical full-length, 42 kb copies of the human *SMN2* gene. Homozygous animals exhibit no overt phenotype through 1 year of age.	HOM	N/A
007963 ★	B6.Cg-*Smn1*^{tm2Mrph}/J	Regeneron A allele-C57BL/6J congenic background	Embryonic lethal	Exons 1-8 of the mouse *Smn1* gene are replaced with *lacZ*. This strain can function as a reporter strain for *Smn1* in the heterozygous state. This allele is a functional null and homozygous animals are embryonic lethal.	HOM	Severe
008713	FVB.129(B6)-*Smn1*$^{tm4(SMN2)Mrph}$/J	Regeneron B allele FVB/NJ congenic background	Embryonic lethal**	This targeted mutation, *Smn* allele B, is a hybrid *Smn1* (survival motor neuron 1) allele in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn1* (survival motor neuron 1) gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene.	HOM	Severe
007955	FVB.Cg-*Smn1*^{tm2Mrph}/J	Regeneron A allele-FVB/NJ congenic background	Embryonic lethal	Exons 1-8 of the mouse *Smn1* gene are replaced with *lacZ*. This strain can function as a reporter strain for *Smn1* in the heterozygous state. This allele is a functional null and homozygous animals are embryonic lethal.	HOM	Severe

008453	B6.129-*Smn1*$^{tm2(SMN2)Mrph}$/J	Regeneron B allele C57BL/6J congenic background	Embryonic lethal	This targeted mutation, *Smn* allele B, is a hybrid *Smn1* (survival motor neuron 1) allele in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn1* (survival motor neuron 1) gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene.	HOM	Severe
008384	B6;129-*Smn1*$^{tm5(Smn1/SMN2)Mrph}$/J	Regeneron C allele mixed genetic background	Viable, no mortality. Homozygous animals exhibit tail necrosis, lower body weight, diminished grip strength, and lower bone mineral content and density with age.	This mutant mouse carries the *Smn* allele C, which contains two tandem *Smn1*/*SMN2* genes. The first is a hybrid gene in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn1* gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene. The second is a full 42 kb copy of the human *SMN2* gene. Homozygous animals exhibit tail necrosis, lower body weight, diminished grip strength, and lower bone mineral content and density with age.	HOM	Mild
007246	B6;129-*Smn1*^{tm2Mrph}/J	Regeneron A allele-mixed genetic background	Embryonic lethal	Exons 1-8 of the mouse *Smn1* gene are replaced with *lacZ*. This strain can function as a reporter strain for *Smn1* in the heterozygous state. This allele is a functional null and homozygous animals are embryonic lethal.	HOM	Severe
008383	B6;129-*Smn1*$^{tm4(SMN2)Mrph}$/J	Regeneron B allele mixed genetic background	Embryonic lethal**	This targeted mutation, *Smn* allele B, is a hybrid *Smn1* (survival motor neuron 1) allele in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn1* (survival motor neuron 1) gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene.	HOM	Severe
008704	B6;129-*Smn1*$^{tm6(SMN2)Mrph}$/J	Regeneron D allele, mixed genetic background	Viable no mortality	*Smn* allele D contains four tandem *SMN* genes. The first is a hybrid gene in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn* gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene. The next three are identical full-length, 42 kb copies of the human *SMN2* gene. Homozygous animals exhibit no overt phenotype through 1 year of age.	HOM	N/A
009381	FVB.Cg-*Smn1*$^{tm6(SMN2)Mrph}$/J	Regeneron D allele, congenic FVB/NJ genetic background	Viable no mortality	*Smn* allele D contains four tandem *SMN* genes. The first is a hybrid gene in which a 2.2 kb segment of mouse genome containing exons 7 and 8 of the mouse *Smn* gene was replaced with a 1.3 kb fragment of human genomic DNA containing exons 7 and 8 of the human *SMN2* gene. The next three are identical full-length, 42 kb copies of the human *SMN2* gene. Homozygous animals exhibit no overt phenotype through 1 year of age.	HOM	N/A
010921	B6.Cg-*Smn1*^{tm1Msd}/J	*Smn1* targeted mutation	Embryonic lethal	This targeted mutant allele was created in the laboratory of Dr. Michael Sendtner at the University of Wurzburg, Germany. Exon 2 of the endogenous mouse *Smn* gene was disrupted by employing a targeting vector encoding a neomycin cassette and a *lacZ* gene fused to the first 40 nucleotides of the disrupted exon to permit expression of the *lacZ* gene in tissues where SMN is normally expressed.	HOM	Severe

* For strains with more than one allele, the genotype designation follows the order of the allele in the strain nomenclature.

Table 3: SMA Strains for Testing Site-Specific SMN Expression (★ Indicates top 5 most frequently used of this strain group)

Stock #	Strain Name	Common Name	Mortality (**unpublished)	General Phenotype	Mutant Genotype*	SMA Type
007951 ★	STOCK *Smn1*$^{tm3(SMN2/Smn1)Mrph}$ Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb/J	Delta 7 mouse with hybrid rescue allele	50% survival at PND 18, 0% survival by PND 22 **	Similar to Stock 005025	HOM-HOM-HOM	Intermediate
008203 ★	STOCK *Smn1*^{tm1Msd} Tg(ACTA1-SMN)63Ahmb Tg(SMN2)89Ahmb/J	HSA63-SMN	Reported average lifespan of 160 days	As an addition to that SMA model, this strain also carries the HSA-SMN transgene; with the human alpha-skeletal actin (HSA or ACTA1) promoter directing full-length human SMN expression at high levels in skeletal muscle. Expression of the HSA-SMN transgene derived from HSA63-SMN founder mice is leaky; with high SMN expression in heart and low SMN expression in spinal cord, brain, and liver. This additional SMN expression in neural cells rescues homozygous; *Smn2; Smn*; HSA63-SMN mice.	HOM-HOM-HOM	Mild
007022 ★	STOCK *Mnx1*$^{tm4(cre)Tmj}$ *Smn1*^{tm1Msd} Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb	Delta 7 mouse carrying Cre	Similar to 005025**	This strain can be used in conjuction with the hybrid rescue allele or the *SMN*^{F7} floxed allele to investigate the role of SMN expression in *Mnx1* expression tissues.	HET-HOM-HOM-HOM	Intermediate
008212 ★	STOCK *Smn1*^{tm1Msd} Tg(Prnp-SMN)92Ahmb Tg(SMN2)89Ahmb/J	PrP92-SMN	Reported average lifespan of 210 days	These animals combine the severe Burghes (005024) model with a prion-promoter driven SMN transgene. When the PrP-SMN transgene is derived from PrP92-SMN founder mice, high SMN expression in spinal cord and brain is observed. Homozygous SMN2; *Smn*; Prp92-SMN mice are rescued from the severe SMA phenotype, have significantly increased lifespan (average of 210 days) and have normal lumbar motor neuron root counts.	HOM-HOM-HOM	Mild
006138 ★	FVB.129(B6)- *Smn1*^{tm1Jme}/J	SMN^{F7}	None reported	This strain carries an *Smn* allele with *loxP* sites flanking exon 7 of murine *Smn1*. This strain can be used in conjunction with variety of Cre lines to examine the effects of knocking out SMN1 expression in a variety of tissues.	HOM	N/A
006146	B6.129-*Smn1*^{tm1Jme}/J	SMN^{F7}	None reported	This strain carries a *Smn* allele with *loxP* sites flanking exon 7 of murine *Smn1*. This strain can be used in conjunction with a variety of Cre lines to examine the effects of knocking out SMN1 expression in a variety of tissues.	HOM	N/A
008209	FVB.Cg-*Smn1*^{tm1Msd} Tg(ACTA1-SMN)69Ahmb Tg(SMN2)89Ahmb/J	HSA69-SMN	Similar to 005024	This strain carries the HSA-SMN transgene; with the human alpha-skeletal actin (HSA or ACTA1) promoter directing full-length human SMN expression at high levels in skeletal muscle. When the HSA-SMN transgene is derived from HSA69-SMN founder mice, skeletal muscle-specific SMN expression is preserved, and homozygous SMN2; *Smn*; HSA69-SMN mutant animals have the same phenotype as homozygous SMA mice.	HOM-HOM-HOM	Severe

007966	B6.Cg-*Smn1*$^{tm3(SMN2/Smn1)Mrph}$/J	Regeneron hybrid rescue allele C57BL/6J congenic background	Embryonic lethal (non-recombined state)	In the non-recombined state this allele is a functional null. Following Cre-mediated irreversible inversion, the allele is converted to the "rescued" format that contains mouse exons 1-7 and human *Smn2* exon 8.	HOM	Severe
007964	FVB.Cg-*Smn1*$^{tm3(SMN2/Smn1)Mrph}$/J	Regeneron hybrid rescue allele FVB/NJ congenic background	Embryonic lethal (non-recombined state)	In the non-recombined state this allele is a functional null. Following Cre-mediated irreversible inversion, the allele is converted to the "rescued" format that contains mouse exons 1-7 and human *Smn2* exon 8.	HOM	Severe
008783	STOCK *Smn*$^{tm3(SMN2/Smn1)Mrph}$ Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb Tg(CAG-cre/Esr1*)5Amc/J	Delta 7 mouse with hybrid rescue allele and tamoxifen inducible Cre	Rescues with TM administration at P4 with some efficacy at P6 and P8. No rescue at P10**	This strain can be used to examine the effects of induced SMN expression at specific developmental time points via the administration of tamoxifen.	HOM-HOM-HOM-HEMI	Intermediate-severe
008359	STOCK *Smn1*$^{tm3(SMN2/Smn1)Mrph}$ Tg(SMN2)89Ahmb/J	Burghes Severe model carrying the hybrid rescue allele	Stillborn or 4-6 days**	This strain can be used in combination with tissue-specific Cre expressing strains to test the effects of site-specific SMN expression in the severe Burghes model (see Stock 005024).	HOM-HOM	Severe
008898	STOCK *Smn1*$^{tm3.1(SMN2/Smn1)Mrpn}$/J	Regeneron hybrid rescue allele in the "rescued" state	Viable no mortality**	Following Ella Cre-mediated irreversible inversion, the allele is converted to the "rescued" format that contains mouse exons 1-7 and human *Smn2* exon 8 in the germline state.	HOM	N/A
010824	STOCK *Smn1*$^{tm3(SMN2/Smn1)Mrph}$ *Smn1*^{tm1Msd} Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb Tg(Sox2-cre)1Amc/J	Delta 7 mouse with hybrid rescue allele and germline expressing Cre	Characterization underway**	This strain can be used to examine the effects of early (embryonic day 6.5) SMN1 expression in the "Delta 7" mouse.	HOM (tm1/tm3) HOM HOM HEMI	Mild
010829	B6.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb *Smn1*^{tm1Msd} *Smn1*$^{tm3(SMN2/Smn1)Mrph}$/J	Type III Burghes mouse on a B6 congenic background carrying the hybrid rescue allele	Characterization underway**	This strain can be used to examine the effects of site-specific or temporal expression of SMN in the A2G mouse model when crossed with a Cre model of choice.	HOM-HOM-HOM (tm1/tm3)	Severe
008897	FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb *Smn1*^{tm1Jme}/J	Delta 7 mouse carrying SMN^{F7}	None reported**	This strain carries an *Smn* allele with *loxP* sites flanking exon 7 of murine *Smn1*. This strain can be used in conjunction with variety of Cre lines to examine the effects of knocking out SMN1 expression in a variety of tissues.	HOM-HOM-HOM	Intermediate
012931	B6.Cg-*Smn1*^{tm1Msd} Tg(Prnp-SMN)92Ahmb Tg(SMN2)89Ahmb/J	PrP92-SMN C57BL/6J congenic	Characterization underway	Characterization underway	HOM-HOM-HOM	Unknown
012935	FVB.Cg-*Smn1*^{tm1Msd} Tg(Prnp-SMN)92Ahmb Tg(SMN2)89Ahmb/J	PrP92-SMN FVB/NJ congenic	Characterization underway	Characterization underway	HOM-HOM-HOM	Unknown

* For strains with more than one allele, the genotype designation follows the order of the allele in the strain nomenclature.

Table 4: SMA Research Tool Strains (★ Indicates top 5 most frequently used of this strain group)

Stock #	Strain Name	Common Name	Mortality (**unpublished)	General Phenotype	Mutant Genotype*	SMA Type
006570 ★	STOCK *Smn1*^{tm1Msd} Tg(Hlxb9-GFP)1Tmj Tg(SMN2)89Ahmb/J	Burghes Severe Model with Hlxb9 GFP reporter	Similar to 005024**	As an addition to Stock 005024, this line carries a transgene containing a Green Fluorescent Protein (GFP) under the direction of the mouse *Hlxb9* promoter. Transgenic mice display distinct expression of GFP in dendrites, axons and soma of spinal motor neurons, allowing identification, isolation and purification of spinal motor neurons by FACS.	HOM-HEMI-HOM	Severe
006553 ★	STOCK *Smn1*^{tm1Msd} Tg(H2-K1-tsA58)6Kio Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb/J	Delta 7 "immorto" mouse	Similar to 005025	This strain combines the Delta 7 mouse model with the immorto mouse transgene and can aid in the development of cell lines for the study of SMA.	HET-HEMI-HOM HOM	Intermediate
016573 ★	FVB.Cg-*Smn1*^{tm1Msd} Tg(S100B-EGFP)1Wjt Tg(SMN2)89Ahmb Tg(SMN2*delta7)4299Ahmb/J	s100 GFP SMA delta 7 mutant	Mean survival ~13 days	This s100 GFP SMA Delta 7 mutant mouse strain may be useful in studies for visualization and vital imaging of neuromuscular junction Schwann cells in the etiology and pathology of SMA.	HOM-HEMI-HOM-HOM	Intermediate
017596 ★	STOCK *Gt(ROSA)26Sor*$^{tm1.1(rtTA,EGFP)Nagy}$ *Smn1*^{tm1Msd} Tg(SMN2)89Ahmb Tg(SMN2*delta7)4299Ahmb Tg(tetO-SMN2,-luc)#aAhmb/J	Delta7 "old" Luci-TRE-SMN	Mean survival ~13 days in the absence of doxycycline administration	These Tg(SMN2)89; *Smn1*$^{-/-}$; Tg(SMNdelta7)4299; *ROSA26*^{rtTA}; "old" Luci-TRE-SMN mice allow high levels of both luciferase and full-length human SMN expression to be regulated by the addition/removal of doxycycline. These may be useful as a fluorescent reporter and/or Tet-On/Tet-Off tool strain for doxycycline-inducible rescue of Type II (moderate) proximal SMA.	HOM-HOM-HOM-HOM-HEMI	Intermediate
017597 ★	STOCK *Gt(ROSA)26Sor*$^{tm1.1(rtTA,EGFP)Nagy}$ *Smn1*^{tm1Msd} Tg(SMN2)89Ahmb Tg(SMN2*delta7)4299Ahmb Tg(tetO-SMN2,-luc)#bAhmb/J	Delta7 "new" Luci-TRE-SMN(B)	Mean survival ~13 days in the absence of doxycycline administration	Similar to Stock 017596. However compared to the "old" pBI-L-SMN construct, the "new" pBI-L-SMN(B) construct used here has a 31 bp sequence (including hemagglutinin epitope tag) deleted between the P_{bi-1} promoter and 5' end of SMN2 cDNA, as well as additional SMN2 exon 8 UTR sequence downstream of the SMN2 cDNA.	HOM-HOM-HOM-HOM-HEMI	Intermediate
017599	STOCK Tg(tetO-SMN2,-luc)#aAhmb/J	"Old" Luci-TRE-SMN	Viable	These Luci-TRE-SMN transgenic mice harbor the "old" pBI-L-SMN transgene designed to express both luciferase and a full-length human SMN gene under the control of a bi-directional tet-responsive promoter. These "old" Luci-TRE-SMN mice allow high levels of both luciferase and full-length human SMN expression to be regulated by the addition/removal of dox.	HEMI	N/A

017600	STOCK Tg(tetO-SMN2,-luc)#bAhmb/J	"New" Luci-TRE-SMN(B)	Viable	These Luci-TRE-SMN transgenic mice harbor the "new" pBI-L-SMN(B) transgene designed to express both luciferase and a full-length human SMN gene under the control of a bi-directional tet-responsive promoter. These "new" Luci-TRE-SMN(B) mice allow high levels of both luciferase and full-length human SMN expression to be regulated by the addition/ removal of dox.	HEMI	N/A
018439	B6.129S6-Tg(CAG-Bgeo,-SMN2) E9Dscd/J	Tg hSMN2 E9 inducible SMN transgenic	Viable	These Tg hSMN2 E9 inducible SMN transgenic mice conditionally express a human SMN2 cDNA. Widespread *lacZ* expression is observed except in those tissues where Cre recombination has resulted in the human SMN2 cDNA to be expressed instead. These transgenic mice are suitable for use in studies related to SMA.	HEMI	N/A

* For strains with more than one allele, the genotype designation follows the order of the allele in the strain nomenclature.

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